Medical research at the cutting edge challenges society's closely held traditions

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Introduction

I have had the experience of working in two major areas of human medicine that have been challenging and rewarding, and have provided some of the most heated debate on medical ethics and disturbance of established social mores. In many respects this made the developments even more difficult because they were frequently and avidly opposed by entrenched religious, political and gender advocates. The medical developments have been extremely successful. In the first place, human in vitro fertilisation (IVF) whose genesis occurred in the 1970s and 1980s has resulted in more than five million births worldwide and can no longer be simply quantified. In some countries with liberal health support systems, more than 3% of all live births are by IVF. The second great quantum development resides in stem cell based therapies, whose influence will be even more pervasive and influential, and whose significance is only just being evaluated in preclinical and clinical trials. This work has evolved from discoveries in bone marrow transplantation in the 1980s and 1990s and embryonic stem cell discoveries between 1998 and 2000.

Human IVF

Why should there have been so many problems in accepting developments that have such benefit to family and to health? In the first place, the moment of conception and first weeks of development were hidden and unable to be scrutinised or manipulated. They were the realms of deep significance in the Catholic religion and the province of control for some radical feminists. This led to strong criticism of IVF because conception was transferred to the laboratory predominantly under the influence of male researchers and clinicians. If the moment of conception is equated with personhood with the entitlement of the complete set of values of a born person, then IVF confers risks and issues that can be problematic. Freezing 4-cell to 100-cell (blastocyst) embryos in the first five to six days of development, their biopsy for inherited genetic disease and their disposal if they are not developing properly or are not required, become issues of conflict. They are, however, also the way in which infertile couples, and those with serious inherited genetic disease, can have a healthy family. Considerable efforts were made to prevent IVF from being provided to patients and even many social commentators decried the technology as being inappropriate as medicine and ineffective as a treatment. Clearly society has largely embraced IVF as an acceptable method of reproduction. Last year my friend and colleague, Robert Edwards, was awarded the Nobel Prize for Physiology for human IVF, a recognition after four decades of our research and medical applications.

Stem Cells

Since 2002, Australian scientists have been permitted to use donated IVF embryos in research. Under the Commonwealth legislation, Research Involving Human Embryos Act 2002, scientists can apply for a license from the National Health and Medical Research Council (NHMRC) to use donated human IVF embryos for stem cell research or research to improve infertility treatments and IVF, provided that the embryos are no longer required for infertility treatment. Additional legislation was also introduced in 2002, the Prohibition of Human Cloning Act 2002, which made it illegal to create, or even attempt to create, a human using cloning technology.

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In 2005, the Australian legislation was reviewed by an independent committee which became known as the 'Lockhart Review' after the late Hon. John Lockhart AO QC who chaired the committee. The committee's recommendations were incorporated into legislation in 2006 following a conscience vote in both Houses of Parliament. The amended legislation – Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006 – specifically allowed Australian researchers to apply for a license to use somatic cell nuclear transfer technology (SCNT, also known as therapeutic cloning) for stem cell research within a strict set of criteria. The amending legislation also increased the penalties associated with any attempts to abuse this technology to clone humans, with reproductive cloning remaining specifically prohibited. The legislation is currently being reviewed by an independent committee who were due to table a report on 27 May 2011.

James Thompson from Wisconsin and our own group at Monash University discovered human embryonic stem cells (ESCs) using methods pioneered by a friend and colleague, Martin Evans, who shared a Nobel Prize for this work. ESCs have the power of immortality and capacity to develop into any cell of the body (pluripotentiality). These characteristics provide these cells with an incredible potential for tissue repair and regeneration. The cells are derived from excess human embryos donated by IVF couples when they no longer wish to use their frozen embryos for reproductive purposes. This created another major social dilemma because the embryos were used

for research and potential therapeutics rather than reproductive purposes. There have been numerous committees formed to protect the sanctity of these donated embryos although patients are permitted to discard (destroy) them if they wish. In the USA, President George W. Bush forbade any further derivation of ESCs with federal funding and President Obama overturned this. Nevertheless, a District Court judge of the District of Columbia found in favour of two scientists who claimed the federal funding of embryonic stem cell research was illegal because of the Dickey-Wicker Amendment, which is usually attached to US budget bills. This was despite President Bush's Administration's prior support of limited research on embryonic stem cells with federal funds. Presently the decision is in appeal but federal funding has all but ceased for new studies.

Is this motivated by ideology and religion? The plaintiffs who brought the action were certainly of this philosophy. The courts are generally conservative but perhaps the appeal will succeed. In the meantime, California raised US$3billion for stem cell research during the Bush Presidency (2004) and as President of this organisation, I am able to support the groundbreaking research that is taking stem discoveries to the clinic for the potential treatment of spinal injury, macular degeneration, type I diabetes, a cure for HIV/AIDS, destruction of inoperable gliobastoma, leukaemias, other solid tumours, inherited sickle cell anaemia, epidermolysis bullosa, stroke and amyotrophic lateral sclerosis (ALS).

Although the roots of ALS are uncertain, three genetic mutations have been linked to it. Researchers had to determine just where the mutations did their dirty work. Were motor neurons damaged by their own genes, or was the damage caused by gene expression in neighbouring cells? The symptoms of ALS appear when motor neurons detach from the muscles they innervate. Using rodents genetically engineered to develop ALS, Dr. Don Cleveland and his team at the University of California, San Diego School of Medicine, first shut off the ALS gene in the motor neurons, but kept it running everywhere else. As expected, the onset of disease was delayed, but there was little meaningful improvement.

The researchers then reversed the experiment, keeping the gene going in the motor neurons, but shutting down its operation in their 'intimate partners', astrocytes. In this case, symptom onset was unchanged, but the disease's progression slowed dramatically. It appears astrocytes with the ALS mutation release a toxin that damages the motor neurons. The animals ended up living twice as long and the team hopes to replace mutant-expressing astrocytes with normal ones in ALS patients.

Life Technologies Corporation of Carlsbad, California, is growing embryonic stem cells and coaxing them to become astrocyte precursor cells that will then be injected into the spinal cords of ALS patients. That trial will begin within four years if animal trials succeed.

Huntington's disease is another affliction that is the target of stem cell researchers. Some 2,000 people are diagnosed with Huntington's every year in the United States. Unlike many inherited diseases, which require two copies of a disease-causing gene to wreak havoc, Huntington's, an autosomal dominant disease, rears its head with a single mutant gene. Therefore, offspring of those with Huntington's have a 50-50 chance of developing the always-fatal disease. In this disease mesenchymal stem cells move from brain cell to brain cell, looking for the injured.

Dr Jan Nolta, Director of the University of California Davis Institute for Regenerative Cures, intends to harness the paramedic services of these bone marrow–derived cells and treat Huntington's disease. Inserted into the brain, these cells actually seek out damage. The errant Huntington's gene is a copy machine run amok, repeating the recipe for the same three nucleic acids 38 times or more. The protein created by this wild repetition, called huntingtin or htt, damages a class of brain cells called medium spiny neurons.

When a medium spiny neuron is healthy, it is shaped something like a spider web, with axons extending in all directions, controlling movement, cognition and emotion. But under huntingtin's influence, it pulls in those axons. Cell-to-cell communication stops, and the person develops involuntary dance-like movements, known as chorea. The condition leads to behaviour changes; a sweet-tempered person becomes irascible. Cognitive function also declines.

To disrupt this destruction, Nolta married the mesenchymal cell's charitable tendencies with a huntingtin-killer. On their own, mesenchymal cells secrete neural growth factors that can restore synaptic connections, though they cannot touch the huntingtin, which continues to plunder. Animal studies, however, showed that strands of RNA can be tailored to cleave the huntingtin RNA, decreasing Huntington's symptoms and prolonging survival. Nolta's team of researchers engineered mesenchymal stem cells to manufacture short interfering RNA, or siRNA. Videos of mesenchymal cells engineered to make this siRNA show cells pouring the siRNA into any sick cells they encounter. Her team has a patent pending on this technology.

The first human studies will use the mesenchymal cells without siRNA, to study the effect of the neural growth factors that mesenchymal stem cells produce. The next study will add the siRNA to the mesenchymal cells.

So how does the balance of potential merit verse ideology influence society in support of new cell based therapies? The community in the US is now 70% supportive of ESCs across all ages and religions. In addition, induced pluripotent stem cells (iPSCs) have been created by Dr. S. Yamanaka using the integration of four transcription factors into adult skin and other cells that solves the ethical dilemma about using ESCs. This was developed on the knowledge of transcription factor activity in human ESCs and provides another incredible new platform for the interrogation of human disease and potential applications in regenerative and personalised medicine. I expect my friends Shinya Yamanaka and John Gurdon (frog nuclear transfer) are likely to win a Nobel Prize for their work on reprogramming cells.

I have had a wonderful career as a research scientist and couldn't have wished for a more fulfilling life. Perhaps some of you will become interested in making new contributions in science and medicine. If you want to make major changes to the status quo, be brave and be prepared for the challenges for interfering with society's closely held traditions.